FUNCTIONAL, SEGREGATED, CHARGED TELODENDRIMERS AND NANOCARRIERS AND METHODS OF MAKING AND USING SAME

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Non-Provisional application Ser. No. 15/759,665, filed on Mar. 13, 2018, which is a National Phase of International Patent Application No. PCT/US2016/051266, filed on Sep. 12, 2016, which claims priority to U.S. Provisional Application No. 62/217,951, filed on Sep. 13, 2015, the disclosure of which is hereby incorporated by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with government support under contract no. 1R01CA140449 awarded by the National Institutes of Health and National Cancer Institute. The government has certain rights in the invention.

FIELD OF THE DISCLOSURE

[0003] The disclosure generally relates to telodendrimers. More particularly the disclosure generally relates to functional, segregated, charged telodendrimers.

BACKGROUND OF THE DISCLOSURE

[0004] Protein therapy is, in a manner, limited by the lack of efficient nanocarriers for intracellular delivery while maintaining protein bioactivity. A rational strategy to create small nanoparticles with high protein loading ability and cell-penetration property is desired but is often overlooked.

[0005] Currently, more than 130 bioactive proteins have been approved to treat human diseases. The majority of these protein therapeutics target the receptors or antigens expressed on the plasma membrane, such as insulin and antibodies. The modification of the pharmacokinetic of the proteins by delivery system is able to enhance their therapeutic efficacy. PEGylation of protein has a long-standing history to efficiently prolong circulation time, increase stability and reduce the immunogenicity of protein therapeutics, especially for recombinant protein therapeutics. Physical encapsulation of proteins into nano- or micro-particles has been intensively studied for systemic or local administration. It is important to maintain protein structure and activity in such protein encapsulation process, especially for the process involving lyophilization or organic solvent applications. For example, the usage of organic solvents in the oil/water emulsion technique for the encapsulation of proteins into biodegradable polymeric microparticles, e.g., polylactic acid and polycaprolactone, usually causes the denaturation of proteins with at least partial losses of activity. Encapsulation of proteins in aqueous environments, such as in hydrogels and nanogels, represents a better way to sustain protein structure and activities. However, these processes mostly relay on polymerization or chemical reactions to crosslink hydrogels at bulky scale or within the nanodispersed aggregates. The chemical process may lead to the complication in control of the physical properties, and the chemicals used in these reactions may present as toxic impurity that hinders application in vivo. Efficient encapsulation of proteins in situ in biologically relevant environments, e.g., pH, temperature and ion strength without extra chemicals or steps needed are highly demanded for clinical development of protein therapeutics.

[0006] Even more proteins are possible to be therapeutics if they can be delivered across plasma membrane into intracellular space, such as antibodies against intracellular proteins used in biochemistry assays or pathology detections. However, such exogenous proteins, even some endogenous proteins are not cell permeable by themselves due to their surface charge distributions, large molecular weights and vulnerable tertiary structures. In addition, they do not have receptors to mediate their intracellular uptake, which renders these proteins inactive. Therefore, the ability to create efficient vehicles for intracellular protein delivery in vivo will expand the horizon dramatically in development and application of therapeutic proteins in disease treatments. The recombinant proteins with targeting domains present solutions for intracellular delivery of such functional proteins. However, the tedious recombinant design/production and the costly process for protein humanization hinder the development of such recombinant therapeutics. Cell-penetrating peptides and cationic polymers/liposomes have been widely studied over the past few decades for intracellular delivery of biomacromolecules, such as genes and proteins while maintaining the bioactivity. However, the advancement of these vehicles are mainly hindered by their positive surface charges, that usually cause high cytotoxicity and are also subjected to nonspecific phagocytosis by the reticuloendothelium systems in vivo. Polymeric vehicles hold great promise to overcome these shortages. The application of microparticles and hydrogels for intracellular protein delivery is limited by their large sizes. The delivery systems based on nano-scaled vehicles are highly promising for intracellular delivery of protein therapeutics to treat human diseases, especially for cancers.

[0007] A recent study by Farokhzad and coworkers showed great promise to minimize zeta potential of the cationic nanocarriers by post-modification of the protein-conjugated nanoparticles with lipid-polyethylene glycol, yielding multinuclear nanoparticles with diameters of 100-150 nm. The protein aggregation and dehydration may likely occur within the big aggregates, which may be irreversible and potentially leads to protein denaturation. In addition, many studies suggested that small particle sizes (10-30 nm) are beneficial for therapeutic delivery with large volume intratumoral distribution and deep tumor penetration. Coating protein with a layer of polymer in aqueous solution is able to address all these concerns to avoid protein aggregation, dehydration and form small particle sizes similar to polymeric micelles (10-30 nm). Optimization of the information encoded in macromolecular building blocks is able to tune the sizes of self-assembled nanoparticles. In a previous study, we observed that the precise control on macromolecular architecture and composition was critical to optimize the particle sizes and drug loading behaviors, which seriously affected the colon cancer treatment efficiency.

SUMMARY OF THE DISCLOSURE

[0008] In an aspect, the present disclosure provides charged telodendrimers. The charged telodendrimers are linear-dendritic copolymers. The charged telodendrimers are functional segregated telodendrimers having, for example, two or three functional segments. In an embodiment, the